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High Prevalence of Anemia among Human Immunodeficiency Virus-Infected Patients: A Cross-sectional Study in Bali-Indonesia

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Anemia is a common condition found among Human Immunodeficiency Virus (HIV)-infected patients. T-cells that are infected with HIV virus can directly suppress the growth of progenitor cells in the bone marrow so that affecting the hemopoiesis resulted in anemia. These hematological abnormalities could potentially cause serious clinical implications. This study was conducted to determine the prevalence of anemia in HIV-infected patients in Bali. It was a hospital-based cross-sectional study conducted at two public hospitals in Bali-Indonesia. A total of 243 medical record data from HIV-infected patients at Widyadharma Hospital Denpasar Bali and Santiaun Hospital Gianyar Bali between 2009-2017 were included in analysis. Prevalence of anemia in antiretroviral (ART)-naïve patients and in patients on ART were 68.8% and 48.3%, respectively. Leucopenia and thrombocytopenia were found 6.2% and 8.4%, respectively, in ART-naïve group. While in patients with ART group leucopenia and thrombocytopenia were accounted for 6.9% and 4.3%, respectively. There was a significant difference in prevalence of anemia between ART-naïve patients and patients on ART (68.8% vs. 48.3%; $p < 0.05$). Although the prevalence of anemia was lower in patients on ART, but anemia continues to be common in a substantial portion of HIV-infected persons. Further studies are still needed to addressing the impact of anemia on HIV-infected individuals, as well as treatment strategies and future research directions.

Keywords: Anemia, Antiretroviral, Bali, HIV, Indonesia.

Anemia is a common hematological abnormalities in patients with human immunodeficiency virus (HIV) infection. The prevalence of anemia among antiretroviral-naïve HIV-infected patients are around 80-90% in India¹. While in Indonesia, the prevalence is much lower which are around 45-60%²⁻⁴. Several studies also documented that anemia to be prevalent in up to

25% among HIV-infected patients treated with antiretroviral⁵⁻⁸.

Several factors are said to account for the anemia in HIV-infected patients. Opportunistic infections and malignancies are known to be major contribution of anemia in HIV. Direct effects of HIV and its viral proteins as well as immune dysregulations during HIV infection were found

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21 Anemia is a common hematological abnormalities in patients with human immunodeficiency virus (HIV) infection. The prevalence of anemia among antiretroviral-naïve HIV-infected patients are around 80-90% in India¹ While in Indonesia, the prevalence is much lower which are around 45-60%^{2,3}. Several studies also documented that anemia to be prevalent in up to

25% among HIV-infected patients treated with antiretroviral⁴⁻⁶

7 Several factors are said to account for the anemia in HIV-infected patients. Opportunistic infections and malignancies are known to be major contribution of anemia in HIV. Direct effects of HIV and its viral proteins as well as immune dysregulations during HIV infection were found



to be responsible for bone marrow suppression. In addition, the emerging role of pro-inflammatory pathways that are also thought to contribute to anemia in HIV infection⁷

Although various studies suggested HIV-related anemia complication improved with antiretroviral therapy, this group of patients still develop mild to moderate anemia. Besides, there are also quality of life impairment reported from anemia HIV-related anemia complication. Antiretroviral regimen and the duration⁷ of antiretroviral therapy were found to be the predictors of anemia in HIV-infected patients treated with antiretroviral. This might be due to Zidovudine toxicity as most patients were in Zidovudine based antiretroviral regimen⁸ Baseline CD4, baseline BMI and duration of zidovudine, female gender, and TB-coinfection were found to be determinant factors for anemia in antiretroviral-treated patients⁹

Several studies reported the prevalence of anemia among HIV-infected patients in Indonesia²⁻¹⁰ However, the magnitude of anemia among HIV patients on antiretroviral are not well documented, especially in ^{11,12}. Thus, this study investigated the prevalence of anemia among HIV infected patients receiving antiretroviral in two referral hospital in Bali, Indonesia.

12

MATERIAL AND METHODS

A hospital based cross-sectional study was conducted on 243 HIV-infected patients at Wangaya Hospital Denpasar Bali and Sanjiwani Hospital Gianyar Bali. Data collection sheet was used to collect the data from ¹³ the patient's medical record between 2009 -2017. The following WHO definition of anemia was used to determined anemia: Hb d¹² (g/dL) for nonpregnant women, Hb d¹¹ (g/dL) for pregnant women, and Hb d¹³ (g/dL) for men.

Cleaning was done before the analysis of the data. Descriptive statistics was used to get clear picture ¹⁴ variables at baseline. The prevalence of anemia was estimated in different subgroups. The group or categorical data were tested for statistical significance using Chi-square test and t-test.

The ethical approval was obtained from Medical Faculty of Udayana University/Sanglah Hospital Research and Ethics Committee before

commencement of study. A formal letter of permission was submitted to Wangaya Hospital VCT Clinic and Sanjiwani Hospital VCT Clinic. Approved was obtained in order to conduct the research in the study sites. Confidentiality was kept by recoding the data with codes and unauthorized person didn't have access to the data.

RESULTS

13

A total of 243 HIV-infected patients were enrolled in this study. At baseline, 171 patients (70%) were HIV-infected patients without antiretroviral therapy (naive) and 72 patients (30%) were HIV-infected patients with antiretroviral therapy. Table 1 gives an overview of patient's baseline characteristics, including sex and age.

Age of patients in this study was in the range of 18-64 years old, with median of age 35 years old. Most of them (68.7%) were in reproductive age group (< 40 years old), both in group of naive treatment (71.3%) and in group with antiretroviral therapy (62.5%). Patients were predominantly male (62.6%), with proportion of 64.9% and 56.9% in naive-treatment group and antiretroviral-treatment group, respectively. Only a small proportion of patients (37.4%) were female and only 76 patients (31.3%) were above 40 years old.

Data from complete blood count examination were ¹⁴ collected. Hematologic parameters such as white blood cell, red blood cell, hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, dan platelet were evaluated. Mean or median of each parameter, both in naive-treatment group and antiretroviral-treatment ²² group, can be seen in Table 2.

Red blood cell count, hemoglobin, mean corpuscular volume and mean corpuscular hemoglobin concentration were significantly different between naive-treatment group and antiretroviral-treatment group ($p < 0.05$; Mann Whitney U Test). White blood cell and platelet count in naive-treatment group were lower than antiretroviral-treatment group, but the difference was not statistically significant ($p > 0.05$).

Based on hematologic parameter described in Table 2, it can be identified some hematologic abnormalities that is anemia, leucopenia, and

thrombocytopenia (Table 3). Anemia is the most common hematologic abnormalities that occurred, both in naive-treatment group (60.8%) and in antiretroviral-treatment group (40.3%). Leucopenia and thrombocytopenia were occurred in smaller proportion, which is 8.2% and 9.4%, respectively, in naive-treatment group. While in antiretroviral-treatment group the proportion of leucopenia and thrombocytopenia was 6.9% and 4.3%, respectively. The prevalence of anemia in naive-treatment group was higher than those in antiretroviral-treatment group (60.8% versus 40.3%, $p < 0.05$). Likewise, the prevalence of leucopenia and thrombocytopenia were higher in naive-treatment group rather than those in antiretroviral-treatment group, but this differences were not statistically significant.

DISCUSSION

Human immunodeficiency virus infection

still a burden in developing countries, including Indonesia. The prevalence of this infection remaining high and still increasing in the past few years. Human immunodeficiency virus type-1 (HIV-1) is the major causative agent of acquired immune deficiency syndrome (AIDS). In Indonesia, especially in Bali, CRF01_AE subtype was the predominant HIV-1 subtype found¹¹

Hematological abnormalities were common among HIV-infected patients. Among them, anemia was the most common complication observed. In this study, prevalence of anemia in naive-treatment group was 60.8%, higher than in antiretroviral-treatment group that was 40.3%. Previous studies revealed that prevalence of anemia in naive-treatment patients ranged from 40%-70%, while in antiretroviral-treatment group the prevalence ranged from 15%-45%^{2,3,6,12,13}

There are several factors that contribute to anemia in HIV-infected patients. Some studies indicate that pathophysiology of anemia in HIV-

Table 1. Baseline characteristics of HIV-infected patients with and without antiretroviral treatment

Characteristics	HIV-infected patients N (%)	Patients without antiretroviral therapy N (%)	Patients with antiretroviral therapy N (%)
Sex			
• Male	152 (62.6)	111 (64.9)	41 (56.9)
• Female	91 (37.4)	60 (35.9)	31 (43.1)
Age			
• <40 years old	167 (68.7)	122 (71.3)	45 (62.5)
• ≥40 years old	76 (31.3)	49 (28.7)	27 (37.5)

Table 2. Hematologic parameters of patients

Hematologic parameter	Patients without antiretroviral therapy	Patients with antiretroviral therapy	p-value
	(n=171)	(n=72)	
White blood cell ($\times 10^3 / \mu\text{L}$)	6.0 ± 2.8	6.4 ± 2.9	0.384
Red blood cell ($\times 10^3 / \mu\text{L}$)	4.3 ± 0.6	4.0 ± 0.8	0.013*
Hemoglobin (g/dL)	12.2 ± 1.8	12.4 ± 2.4	0.039*
Hematocrit (%)	36.4 ± 5.3	37.1 ± 7.1	0.052
Mean corpuscular volume (L)	84.8 ± 9.1	95.2 ± 11.4	0.000**
Mean corpuscular hemoglobin (pg)	28.6 ± 2.3	32.1 ± 4.3	0.000**
Mean corpuscular hemoglobin concentration (%)	33.5 ± 1.7	33.7 ± 1.6	0.27
Platelet ($\times 10^3 \text{ uL}$)	249.5 ± 100.2	261.4 ± 87.7	0.148

* $P < 0.05$; ** $P < 0.01$

Table 3. Hematologic abnormalities among HIV-infected patients with and without antiretroviral treatment

Hematologic abnormalities	Patients without antiretroviral therapy (n=171)	Patients with antiretroviral therapy (n=72)	p-value
Anemia	104 (60.8)	29 (40.3)	0.003*
-Mild	88 (51.5)	22 (30.6)	
-Moderate	12 (7.0)	4 (5.6)	
-Severe	4 (2.3)	3 (4.2)	0.742
Leucopenia	14 (8.2)	5 (6.9)	
-Mild	6 (3.5)	4 (5.6)	
-Moderate	6 (3.5)	0	0.185
-Severe	1 (0.6)	1 (1.4)	
Trombositopenia	16 (9.4)	3 (4.3)	
-Mild	11 (6.4)	1 (1.4)	
-Moderate	2 (1.2)	0	
-Severe	3 (1.8)	2 (2.8)	

*P<0.05

infected patients may a result of direct effect of virus itself. HIV infection results changes in cytokine production with subsequent effects on hematopoiesis. The virus inhibit hematopoietic progenitor cell survival and proliferation, thus also result in erythrocyte differentiation impairment. In addition, HIV infection also effect on stromal cell with cytokine dysregulation and development of autoantibodies to erythropoietin and erythrocyte¹⁴.¹⁵ In other circumstances, HIV itself also influences the mtDNA contents and cause toxicity as a result of chronic HIV inflammation¹⁶

The other factor that contribute to anemia in HIV-infected individual was CD4 count. Previous studies indicated that the frequency and severity of anemia increased in line with decline in CD4 count^{4, 17, 18}. CD4 is a cell receptor carried by T-helper lymphocytes and monocytes commonly present in the bone marrow. This receptor is found on the cell surface that is the target of HIV. HIV infection on monocyte cell in the bone marrow alter the release of cytokines, which indirectly suppress the capacity of hemopoietic progenitor cells to respond adequately to anemia. This mechanism explain why the severity of anemia increased in line with decline in CD4 count^{7, 14, 19}. Other studies exploring risk factors of anemia in HIV-infected patients revealed that nutritional status and

opportunistic infections also have contribution to anemia in this group of patients¹⁵

In the present study, the prevalence of anemia in antiretroviral-treatment group was 40.3%. This result was similar with study conducted by Akilimali *et al* that reported up to 43% patients remain anemic after 12 month of antiretroviral therapy¹³. Another study in Ethiopia shown the lower prevalence of anemia after 12 month of antiretroviral therapy, that is around 14%⁶. Antiretroviral therapy contributes to anemia resolution in many studies^{4, 5, 12, 20}. However in some cases HIV infected patients cannot always be resolved with durable efficient antiretroviral therapy. It is possibly due to residual inflammation or immune activation rather than unbalanced iron homeostasis²¹. Study conducted by Ishultz *et al* reported that having hemoglobin <14 g/dL for men and <13 g/dL for women was independently associated with monocyte activation in HIV-infected adults on stable antiretroviral therapy. It has been shown that even after suppressing HIV with antiretroviral, persistent systemic inflammation and activation of the immune system occur²²

The prevalence of having mild anemia in this study was 30.6%. This results are congruent with another studies that reported at least 33% of

patients with antiretroviral therapy experienced mild anemia²². Although this is slightly higher than in a recent cross-sectional study of HIV-infected adults on ART, the SILCAAT study, the discrepancy is likely due to the different definition used for anemia²³.

CONCLUSION

The magnitude of anemia among HIV-infected patients was variable based on the study settings and the definition of anemia. Treatment with antiretroviral contributes to anemia resolution due to the positive effect of antiretroviral on the differentiation and survival of erythrocytes. In spite of this, the overall burden of anemia in ART treated patients remains high. Although the prevalence of anemia was lower in patients receiving antiretroviral, but anemia continues to be common in a substantial portion of HIV-infected persons. Another studies are still needed to addressing the impact of anemia on HIV-infected individuals, as well as treatment strategies and future research directions.

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Conflict of interest

We have no conflicts of interest to disclose.

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